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FEATURES OF PROCALCITONIN AND C-REACTIVE PROTEIN IN PROLONGED NEONATAL HYPERBILIRUBINEMIA.

Boboeva Nigora Tukhtamishevna.
Samarkand State Medical University,
Republic of Uzbekistan, Samarkand.

Summary: *The article presents the causal mechanisms of long-term neonatal hyperbilirubinemia. Modern methods of studying inflammatory markers are described. Early signs of inflammatory activity in chronic hyperbilirubinemia of rats.*
Key words: *bilirubin, hyperbilirubinemia, procalcitonin, C-reagent oxil.*
The scientific work presents the causal mechanisms of prolonged neonatal hyperbilirubinemia. The modern methods of studying inflammation markers are described. The early markers of inflammatory activity in prolonged hyperbilirubinemia were analyzed.

Introduction.

Hyperbilirubinemia in newborns has become more prolonged in recent decades. Reasons but this phenomenon is not clear[1]. [1]. A certain part of these conditions are transient for the child and do not require special correction, however, in some cases, neonatal hyperbilirubinemia takes a protracted course, resulting in a high risk of developing complications caused by the neurotoxicity of indirect bilirubin[2][2,3].

Currently, the problem of jaundice in newborns is gaining new relevance in connection with the observed pathomorphosis of perinatal pathology4 [4].The prevalence and high frequency

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of damage to organs and systems in neonatal jaundice is of interest to clinicians and practitioners in the range of identifying the leading cause of the development of this pathology in a particular case. In the differential diagnosis of neonatal jaundice, markers of inflammatory activity are increasingly important. [5,8,9].

Markers of inflammatory activity serve as one of the confirmatory factors in the absence of a positive bacterial culture. CRP is considered one of these markers, but the search for new markers has proven that procalcitonin [3,2,4,6,7] as a precursor of calcitonin is highly sensitive during infection [4,10,11,12,13,14,15, 16,17].

Purpose of the study: use of inflammatory markers to isolate the cause of prolonged hyperbilirubinemia.

Materials and methods of research. In this study 250 newborns with prolonged neonatal hyperbilirubinemia (PNH) were observed. All newborns with PNH were admitted for treatment and examination at the acute care unit of the Samarkand Regional Multidisciplinary Children's Medical Center. In all cases, hyperbilirubinemia lasted more than 14 days.

The study did not include newborns with serious anomalies of the hepatobiliary system or patients who required surgical treatment; newborns with hereditary types of neonatal hyperbilirubinemia.

The condition of all newborns upon admission was assessed as moderately severe, which was due to the presence of hyperbilirubinemia, which was assessed using a modified Cramer scale of 3–4 degrees.

Newborns were admitted to the clinic 15–20 days after birth. Depending on the clinical signs and serum bilirubin level in prolonged neonatal hyperbilirubinemia (PNH), all newborns were divided into 2 groups:Group I - with moderate prolonged hyperbilirubinemia (bilirubin level not more than 250.0 μmol/l); Group II – with prolonged high-grade hyperbilirubinemia (bilirubin level 250.0-270.0 μmol/l, prolonged in nature with a duration of more than 21 days). Group I included 34.0% (n=85) of newborns, group II included 46.0% (n=115) of newborns. Group III – control 20% (n=50). The group of observed children represented158 boys (63.2%) and 92 girls (36.8%).All children were born at term (38-40 weeks of gestation). 90.0% were from physiological births, 10.0% of children were by cesarean section.

The gestational age of the observed group of newborns was 38.15±1.07 weeks. Newborns were selected on the basis of clinical and biochemical parameters. The basis of diagnostic measures included the sum of factors that prove a direct clinical connection with PNH. Of these: anemia in pregnant women, diseases of the biliary tract in the mother, perinatal losses, severe gestosis, recurrent miscarriage, premature placental abruption, spontaneous miscarriages, as well as various

complications of childbirth: weakness of labor, rapid labor, entanglement of the newborn with the umbilical cord.

Analysis of the obstetric history and health status of women indicated an extremely high level of obstetric and somatic pathology. 65% of the observed women were primigravidas, with a burdened obstetric history: 24% had spontaneous miscarriages, 16.4% had regressing pregnancies, 5.5% had stillbirths. By the time of the actual pregnancy, all women were in a state of compensation for chronic diseases.

To identify the causes of neonatal hyperbilirubinemia, we used generally accepted biochemical tests: blood bilirubin and its fractions, transaminases, total protein, albumin, electrolyte content. An analysis of "acute phase" proteins was also carried out - C - reactive protein (CRP). CRP was determined in serum using CYPRESS DIAGNOSTICS. The test is based on the principle of solid-phase indirect enzyme immunoassay.

The level of procalcitonin (PCT) in blood serum was determined by immunochromatographic method using test systems produced by Brahms Diagnostica, (Germany). Informed consent from parents was obtained for the examination of newborns.

Results and their discussions.

In the newborns studied, hyperbilirubinemia was the main indicator for hospitalization. The data obtained showed that newborns with PNH were characterized by visual changes in the skin, in the form of prolonged jaundice, which is what most groups of parents addressed. Visually, subicteric skin and mucous membranes in newborns with PNH often appeared on days 3-4 of life: in 36.1% - on the third day, in 42.5% - on the fourth. In 9.9% of newborns, jaundice appeared on the second day of life, in 10.3% on the fifth, and in 1.2% on the sixth day of life. In PNH, subicteric skin and mucous membranes had a wave-like appearance of jaundice.

Taking into account the severity of hyperbilirubinemia according to the modified Cramer scale, we previously distributed the levels of hyperbilirubinemia depending on the concentration of serum bilirubin in the blood serum (Figure 1).

Fig 1

Cramer scale M±SD

Serum total bilirubin level	Group I	II group	III group	Group I	SD	Confidence in %	II group	SD	Confidence in %	III group	SD	Confidence in %
		M±m			M±m			M±m				
80-150 µmol/l	19	-	6	132.32±2.79	12.18	2.11	-	-	-	133.33±10.54	25.81	7.9

150-200 µmol/l	25	-	25	180.24±2.6	13.02	1.44	-	-	-	177.24±2.59	12.94	1.46
200-250 µmol/l	40	-	13	226.62±2.18	14.1	0.96	-	-	-	232.31±3.68	13.27	1.58
more than 250 µmol/l	1	115	6	-	-	-	274.83±3.08	7.54	1.12	330.6±5.92	63.2	1.79

In all examined groups of newborns, there was no increase in the activity of serum aminotransferases.

Children with prolonged level 1 hyperbilirubinemia in 96.9% had a slight icteric tint of the face and chest already on days 14-16 of life; in newborns with prolonged neonatal hyperbilirubinemia levels 2 and 3, this indicator was observed only by days 20-23. On the twenty-third day, a decrease in skin jaundice to grade 1 was not observed in newborns of the second group; a later disappearance of jaundice was noted: only by the 25-30th day of life in 11.6% of children from the second group, the level of icterus decreased to grade 1, and the disappearance of jaundice in 58.5% of cases occurred by the end of 4-5 weeks of life, in 20.1% - only by a month.

As you can see, the number of newborns with level 2 hyperbilirubinemia in all studied groups is greater than the number of children with a bilirubin level of less than 170 µmol/l. The number of children with level 3 hyperbilirubinemia is significantly less than with level 1 hyperbilirubinemia.

In general, hyperbilirubinemia up to 257 µmol/l was observed in 50.5% of newborns.

In our observations, in newborns with prolonged hyperbilirubinemia due to intrauterine infection and hypoxic ischemic encephalopathy due to infection, a syndrome of central nervous system depression was noted, manifested in the form of sluggish sucking, decreased motor activity, muscle hypotonia, hyporeflexia, and exhaustion of physiological reflexes. It occurred in 68% of newborns. CNS hyperexcitability syndrome – in 9.1% and 10%, respectively.

The results of clinical studies showed that initially the patients had severe disturbances in the metabolic parameters of venous blood (hyperbilirubinemia more than 250-300 µmol/l, hypoalbuminemia, glucose less than 1.9 units, hyperkalemia 45 mmol/l).

Due to the fact that infectious pathology was one of the common causes of PNH for differential diagnosis based on etiology, C-reactive protein was studied in all newborns (Fig. 2).

Figure 2

Serum CRP level

Index	**Study group**	

	Group I, n=85				Group II, n=115				Control group				Significance of differences between groups		
(10mg/l)	n	M±m	SD	Confidence in %	n	M±m	SD	Confidence in %	n	M±m	SD	Confidence in %	I-II	I-III	II-III
0-15	48	10.89±0.32	2.65	3.51	51	11.09±0.38	2.7	3.4	47	7.7±0.39	2.73	5.17	p>0.05	p<0.05	p<0.05
15-20	24	18.88±0.25	1.22	1.33	21	19±0.23	1.07	1.25	3	18.33±0.88	1.53	4.81	p>0.05	p<0.05	p<0.05
20-25	10	22.9±0.38	1.19	1.65	20	23.05±0.27	1.23	1.2	-	-	-	-	p>0.05	-	-
>25	3	34.67±6.69	11.59	19.3	23	30.04±0.56	2.68	1.86	-	-	-	-	p>0.05	-	-

The observed increase in C-reactive protein (CRP) levels with normal PCT values (Figure 3) indicates the onset of the development of inflammation of non-infectious (adaptive) origin [18,19].

Figure 3

Serum PCT value

Index	Study group												Significance of differences between groups		
	Group I, n=85				Group II, n=115				Control group						
(0.1-1.0 ng/l)	n	M±m	SD	Confidence in %	n	M±m	SD	Confidence in %	n	M±m	SD	Confidence in %	I-II	I-III	II-III
0-0.3	51	0.19±0.01	0.09	6.33	52	0.19±0.01	0.09	6.58	39	0.21±0.01	0.08	6.22	p>0.05	p<0.05	p<0.05
0.3-1	29	0.48±0.007	0.04	1.51	54	0.5±0	0	0	eleven	0.47±0.01	0.05	2.97	p<0.05	p<0.05	p<0.05
1-5	5	2.7±0.58	1.3	21.59	9	2.33±0.33	1	14.28	-	-	-	-	p>0.05	-	-

Of the 100 newborns with PNH examined, procalcitonin was elevated, i.e. above 0.5 ng/ml, only in 3 patients from groups 2 and 3. In other newborns, PCT was not increased. This does not coincide with the literature data [4,5,9,18,19] on the high sensitivity of PCT in the

presence of inflammatory activity, while the level of CRP is increased and leukocytosis is observed.

Conclusions

Analysis of inflammatory activity in PNH does not emphasize the role of inflammation in the development of PNH, namely, the PCT level as an indicator of the inflammatory marker in both groups within the normal range against the background of moderate fluctuations in C-reactive protein against the background of a low LII against the background of a high IIR does not highlight the leading role of inflammatory activity prolonged neonatal hyperbilirubinemia.

In case of prolonged neonatal hyperbilirubinemia against the background of infection, a high level of CRP and leukocytosis are more reliable as markers of inflammation than procalcitonin.

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